What is claimed is:

1. A method of detecting infectious disease minority variants, comprising:

contacting a nucleic acid sample from a subject or a cell with at least one oligonucleotide pair to form a reaction mixture, wherein a pair comprises a first (P1) and a second (P2) oligonucleotide, wherein P1 comprises a first gene specific region and a first primer region, P2 comprises a second gene specific region and a second primer region; either P1 or P2 comprise a detection region; either P1 or P2 comprise a nucleotide difference in the gene specific region; and P1 and P2 are suitable for ligation to one another;

subjecting the reaction mixture to a ligation reaction; and

amplifying a ligation product to form a reaction product.

2. The method of claim 1, wherein the minority variant is viral or microbial.

3. The method of claim 1, wherein the viral minority variant is HIV, HBV, HCV, CMV, influenza, HSV, RSV, or VZV.

4. The method of claim 3, wherein the viral minority variant is a viral drug-resistant minority variant.

5. The method of claim 1, wherein the nucleotide difference detected encodes one or more of the amino acid changes K103N, Y181C, K103E, K103R, K103T, G190A, P236L, or another substitution in the viral genome associated with altered susceptibility to one or more antiviral drugs.

6. A method of differentiating pancreatic cancer from chronic pancreatitis comprising:

contacting a nucleic acid sample from a subject or a cell with at least one oligonucleotide pair to form a reaction mixture, wherein a pair comprises a first (P1) and a second (P2) oligonucleotide, wherein P1 comprises a first gene specific region and a first primer region, P2 comprises a second gene specific region and a second primer region; either P1 or P2 comprise a detection region; either P1 or P2 comprise a

nucleotide difference in the gene specific region; and P1 and P2 are suitable for ligation to one another;

subjecting the reaction mixture to a ligation reaction; and

amplifying a ligation product to form a reaction product.

7. The method of claim 6, wherein the nucleotide difference is in KRAS2.

8. The method of claim 7, wherein the KRAS2 nucleotide difference is one or more of G35A, G35T, G35C, G34A, G34T, G38A, or A182T.

9. The method of claim 6, further comprising analyzing the reaction product.

10. The method of claim 6, further comprising determining the KRAS mutation level.

11. The method of claim 6, wherein a mutation level of less than about 0.6% indicates chronic pancreatitis.

12. The method of claim 6, wherein a mutation level of from between about 0.5% to about 80% indicates pancreatic cancer.

13. The method of claim 6, further comprising monitoring the KRAS mutation levels.

14. A method of diagnosing a disease in a subject comprising:

obtaining a biological sample from a subject;

contacting the biological sample with at least one oligonucleotide pair to form a reaction mixture, wherein a pair comprises a first (P1) and a second (P2) oligonucleotide, wherein P1 comprises a first gene specific region and a first primer region, P2 comprises a second gene specific region and a second primer region; either P1 or P2 comprise a detection region; either P1 or P2 comprise a nucleotide difference in the gene specific region; and P1 and P2 are suitable for ligation to one another;

subjecting the reaction mixture to a ligation reaction; and

amplifying a ligation product to form a reaction product.

15. The method of claim 14, wherein the disease is a disease caused by, induced by or related to a nucleotide difference in at least one gene.

16. The method of claim 14, wherein the disease is Parkinson's disease, Duchenne muscular dystrophy, Niemann-Pick disease, polyposis, neurofibromatosis, polycystic kidney disease, Tay-Sachs disease, xeroderma pigmentosa, ataxia-telangiectasia, Huntington disease, Li-Fraumeni syndrome, beta-thalassemia, sickle cell anemia, hemoglobin C disease, hemophilia, acute intermittent porphyria, cystic fibrosis, diabetes, obesity, cardiovascular disease, cancer, chronic pancreatitis, cerebrovascular disease, respiratory disease, influenza, pneumonia, Alzheimer's, infectious disease, septicemia, liver disease, or hypertension.

17. The method of claim 16, wherein the cancer is leukemia, lymphoma, melanoma, neuroblastoma, retinoblastoma, rhabdomyosarcoma, Ewing sarcoma, head and neck cancer, skin cancer, melanoma, brain cancer, esophageal cancer, stomach cancer, lung cancer, breast cancer, colon cancer, ovarian cancer, testicular cancer, pancreatic cancer, prostate cancer, rectal cancer, bladder cancer, renal cancer, uterine cancer, thyroid cancer, liver cancer, biliary cancer, bronchial cancer, laryngeal cancer or testicular cancer.

18. The method of claim 14, wherein the disease is a residual disease.

19. The method of claim 14, wherein the diagnosis is for early detection.

20. The method of claim 14, wherein the diagnosis is molecular relapse.

21. The method of claim 14, wherein the determination is to predict chemosensitivity or chemoresistance.

22. The method of claim 14, wherein the subject is a fetus and the diagnosis is a prenatal diagnosis.

23. A method of forensic identification, comprising:

obtaining a nucleic acid forensic sample;

contacting a nucleic acid forensic sample with at least one oligonucleotide pair to form a reaction mixture, wherein a pair comprises a first (P1) and a second (P2) oligonucleotide, wherein P1 comprises a first gene specific region and a first primer region, P2 comprises a second gene specific region and a second primer region; either P1 or P2 comprise a detection region; either P1 or P2 comprise a nucleotide difference in the gene specific region; and P1 and P2 are suitable for ligation to one another;

subjecting the reaction mixture to a ligation reaction; and

amplifying a ligation product to form a reaction product.

24. The method of claim 23, wherein the forensic sample is from a crime scene.

25. The method of claim 23, wherein the forensic nucleic acid sample is derived from a biological sample.

26. The method of claim 23, further comprising comparing the reaction product to a reference nucleic acid sequence.

27. The method of claim 26, wherein the reference nucleic acid sequence is from a family member, a suspect, a person of interest, or a standard.

28. A method of identifying a sample containing an uncommon genetic change, comprising:

obtaining a pooled nucleic acid sample;

contacting the pooled sample with at least one oligonucleotide pair to form a reaction mixture, wherein a pair comprises a first (P1) and a second (P2) oligonucleotide, wherein P1 comprises a first gene specific region and a first primer region, P2 comprises a second gene specific region and a second primer region; either P1 or P2 comprise a detection region; either P1 or P2 comprise a nucleotide difference in the gene specific region; and P1 and P2 are suitable for ligation to one another;

subjecting the reaction mixture to a ligation reaction; and

amplifying a ligation product to form a reaction product.

29. The method of claim 28, wherein the pooled nucleic acid sample is a pool of samples.

30. The method of any one of claims 1, 6, 14, 23, or 28, wherein the mutated gene specific region is at the 3'end of P1 and/or the 5' end of P2.

31. The method of any one of claims 1, 6, 14, 23, or 28, wherein the mutated gene specific region is the 3' nucleotide of P1 or the 5' nucleotide of P2.

32. The method of any one of claims 1, 6, 14, 23, or 28, wherein the mutated gene specific region is within the 3' five nucleotides of P1 or the 5' five nucleotides of P2.

33. The method of any one of claims 1, 6, 14, 23, or 28, wherein the mutated gene specific region is between about 1 and about 5 nucleotides in length.

34. The method of any one of claims 1, 6, 14, 23, or 28, wherein the mutated gene specific region is between about 5 and about 30 nucleotides in length

35. The method of any one of claims 1, 6, 14, 23, or 28, wherein P1 and P2 ligate only if the nucleotide difference is present in the nucleic acid sample.

36. The method of any one of claims 1, 6, 14, 23, or 28, wherein the contacting the nucleic acid sample with a third (P3) and a fourth (P4) oligonucleotide wherein P3 comprises a third gene specific region and a third primer binding region and P4 comprises a probe binding region, a fourth primer binding region, a fourth gene specific region and a second mutated gene specific region.

37. The method of any one of claims 1, 6, 14, 23, or 28, wherein the contacting the nucleic acid sample with a third (P3) wherein P3 comprises a probe binding region unique from P2, a primer binding region, a third gene specific region that targets the wild-type version of the gene.

38. The method of any one of claims 1, 6, 14, 23, or 28, wherein the contacting the nucleic acid sample is with a fifth (P5) and a sixth (P6) oligonucleotide wherein P5 comprises a fifth gene specific region and a fifth primer binding region and P6 comprises a probe binding region, a sixth primer binding region, a sixth gene specific region, and a third mutated gene specific region.

39. The method of any one of claims 1, 6, 14, 23, or 28, wherein the contacting the nucleic acid sample is with 4 to 1000 oligonucleotide pairs wherein one of each pair comprises a gene specific region and a primer binding region, while the other in the pair comprises a probe binding region, a primer binding region, a gene specific region, and a mutated gene specific region.

40. A method of detecting a nucleic acid sequence difference, comprising:

contacting a nucleic acid sample with at least one oligonucleotide pair, wherein a pair comprises a first (P1) and a second (P2) oligonucleotide, wherein P1 and P2 bind to a nucleic acid to form a reaction mixture, and wherein P1 comprises a first gene specific region and a first primer binding region and P2 comprises a probe binding region, a second primer binding region and a second gene specific region, wherein there is a gap of one or more nucleotides between the first and second gene specific regions contains the nucleic acid difference;

providing the reaction mixture with a nucleotide complementary to the nucleotide differencenucleic acid difference;

subjecting P1, P2, and the nucleotide to ligation conditions to form a ligation product; and

amplifying the ligation product to form a reaction product.

41. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the nucleic acid difference is one or more of KRAS2 nucleotide difference, K103N HIV-1 drug-resistance nucleotide difference, CFTR nucleotide difference, p53 nucleotide difference, or Braf nucleotide difference.

42. The method of claim 41, wherein the nucleotide ligates to one or more of P1 or P2 if the nucleotide difference is present.

43. The method of claims 1, 6, 14, 23, 28 or 40, wherein the nucleic acid difference is a base substitution, single nucleotide polymorphism, microsatellite, transversion, transition, missense mutation, nonsense mutation, insertion, deletion, frameshift mutation, internal tandem repeat, amplification, translocation, germline mutation, somatic mutation or altered methylation.

44. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein P1 and P2 are between about 10 and about 140 nucleotides in length.

45. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the first and second gene specific regions are between about 10 and about 100 nucleotides in length.

46. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the first or the second primer regions comprise one or more of an M13 forward, M13 reverse, T7, SP6, T3, lambda gt10 forward, lambda gt10 reverse, lambda gt11 forward, lambda gt11reverse, DNA zipcode, address code, DNA barcodes, DNA tags or DNA anti-tag sequences.

47. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein analyzing is by bead hybridization, rolling circle amplification, hyperbranching rolling circle amplification, ligase chain reaction, strand displacement amplification, transcription mediated amplification, or nucleic acid sequence base amplification.

48. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the analyzing is by real time quantitative PCR, Taqman probing, molecular beacons, FRET hybridization probes, scorpion probes, Sybr green, or melting curve analysis.

49. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the detection region is a probe binding region.

50. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the probe binding region is a known DNA sequence that is not complementary to the sequence up-stream and down-stream of the gene specific regions and the mutated gene specific region.

51. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the analyzing is with a probe complementary to the probe binding region.

52. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the detection region is a known nucleotide sequence that is not complementary to the sequence up-stream and down-stream of the gene specific regions and the mutated gene specific region.

53. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the detection region is one or more of a lacZ sequence, 16S rDNA sequence, M13 forward, M13 reverse, T7, SP6, T3, lambda gt10 forward, lambda gt10 reverse, lambda gt11 forward, lambda gt11reverse, DNA zipcode, address code, DNA barcodes, DNA tags or DNA anti-tag sequences.

54. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the detection region contains a labeled nucleotide.

55. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the labeled nucleotide is fluorescent, radioactively, chemical moiety or colorimetricly labeled.

56. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the nucleic acid sample is plasmid DNA, genomic DNA, PCR product, mitochondria DNA, RNA, DNA virus, RNA virus or a cell.

57. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the amplifying is by PCR, quantitative PCR, real time PCR, or real time quantitative PCR.

58. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the amplifying is quantitative.

59. The method of any one of claims 1, 6, 14, 23, 28 or 40, further comprising removing unbound P1 and P2 prior to amplifying.

60. The method of any one of claims 1, 6, 14, 23, 28 or 40, further comprising providing a nucleic acid sample.

61. The method of any one of claims 1, 6, 14, 23, 28 or 40, further comprising amplifying genomic DNA to produce a nucleic acid sample.

62. The method of claim 53, wherein the amplifying is by PCR, real-time PCR, rt-PCR, real time rt-PCR, Q-PCR,Taqman probing, molecular beacons, FRET hybridization probes, scorpion probes Sybr green, or melting curve analysis.

63. The method of any one of claims 1, 6, 14, 23, 28 or 40, further comprising analyzing the reaction product.

64. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein analyzing is by performing chromatography, capillary electrophoresis, microfluidic analysis, slab gel electrophoresis, intercalating agent, Southern blot real-time PCR, surface plasmon resonance, flow cytometry, fluorescence polarization, hybridization, microarray detection, or radiography.

65. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the intercalating agent is ethidium bromide or an unsymmetrical cyanin dye.

66. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the amplifying is bottom strand synthesis.

67. The method of any one of claims 1, 6, 14, 23, 28 or 40, further comprising Q-PCR probe cleavage after the amplification of the ligation product.

68. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the nucleic acid sample contains from between about a 1:1 to about a 1:1,000,000 ratio of mutated nucleic acid to wild type nucleic acid.

69. The method of any one of claims 1, 6, 14, 23, 28 or 40, further comprising providing one or more of a DNA, RNA, LNA, PNA probe complementary and overlapping with the wild-type allele to the ligation reaction.

70. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein a target nuclic acid has two strands and wherein a pair of oliginuclietides is directed to both nucleic acid strands.

71. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the subject is a mammal.

72. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the mammal is a human.

73. The method of any one of claims 1, 6, 14, 23, 28 or 40, wherein the biological sample is one or more of pancreatic duct juice, peripheral blood, serum, plasma, skin, urine, feces, tears, mucus, sputum, bile, sweat, or fine needle aspirate.

74. The method of claim 40, wherein the method is operable to detects infectious disease minority variants, differentiates pancreatic cancer from chromic pancreatitis, diagnoses a disease, or forensically identifies samples.

75. A kit for one of more of detecting infectious disease minority variants, differentiating pancreatic cancer from chromic pancreatitis, diagnosing a disease, forensic identification, comprising:

at least one first (P1) and at least one second (P2) oligonucleotide to form a reaction mixture, wherein P1 comprises a first gene specific region and a first primer region, P2 comprises a second gene specific region and a second primer region; either P1 or P2 comprise a detection region; either P1 or P2 comprise a nucleotide difference in the gene specific region; and P1 and P2 are suitable for ligation to one another; and

instructions for use.

76. A kit for one of more of detecting infectious disease minority variants, differentiating pancreatic cancer from chromic pancreatitis, diagnosing a disease, forensic identification, or detecting a nucleic acid sequence difference, comprising:

at least one first (P1) and at least one second (P2) oligonucleotide, wherein P1 and P2 bind to a nucleic acid to form a reaction mixture, and wherein P1 comprises a first gene specific region and a first primer binding region and P2 comprises a probe binding region, a second primer binding region and a second gene specific region, wherein there a nucleotide gap between the first and second gene specific regions contains the nucleic acid difference; and

instructions for use.